ACUTE TOXICITY SUMMARY

ETHYLENE GLYCOL MONOMETHYL ETHER

(2-methoxyethanol, 1-hydroxy-2-methoxyethane, methyl cellosolve)

CAS Registry Number: 109-86-4

I. Acute Toxicity Summary (for a 6-hour exposure)

Inhalation reference exposure level	**93 µg/m³**
Critical effect(s)	teratogenic effects
Hazard Index target(s)	Reproductive/developmental

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

Description	colorless liquid
Molecular formula	$C_3H_8O_2$
Molecular weight	76.09
Density	0.965 g/cm^3 @ 20°C
Boiling point	125°C
Melting point	-85.1°C
Vapor pressure	6.2 mm Hg @ 20°C
Flashpoint	41.7° C (closed cup) (ACGIH, 1991)
Explosive limits	upper = 19.8% (ACGIH, 1991) lower = 2.5% (ACGIH, 1991)
Solubility	miscible with water, alcohol, benzene, ether, acetone
Odor threshold	2.3 ppm (Amoore and Hautala, 1983)
Odor description	mild ethereal odor
Metabolites	methoxyacetic acid, carbon dioxide (Miller *et al*., 1983)
Conversion factor	1 ppm = 3.1 mg/m³ @ 25°C

III. Major Uses or Sources

Ethylene glycol monomethyl ether (EGME) is used as a solvent for cellulose acetate and resins (HSDB, 1994). It is also used in dyeing leather and in the manufacture of photographic film. EGME is used as an antifreeze in jet fuels. Quick drying varnishes, enamels, nails polishes and wood stains may also contain EGME.

IV. Acute Toxicity to Humans

Acute overexposure to EGME may cause irritation of the eyes, nose, and throat, drowsiness, dizziness, headache, nausea, vomiting, disorientation, and loss of consciousness (HSDB, 1994). Fatigue and hematologic effects including decreased white and red blood cell counts, and decreased hemoglobin, hematocrit and platelet levels, were observed in a microfilm manufacturing worker following daily inhalation exposure for approximately 9 months to a mean concentration

of 35 ppm EGME and substantial but unquantified dermal exposure (Cohen, 1984). Concomitant exposure to methyl ethyl ketone and propylene glycol monomethyl ether was also reported.

Retention of EGME was reported to be 76% in seven male volunteers who inhaled 5 ppm EGME for 4 hours (Groeseneken *et al*., 1989). The average elimination half-life was 77 hours. The majority (85%) of the inhaled dose was metabolized to methoxyacetic acid.

Predisposing Conditions for EGME Toxicity

Medical: Persons with eye, neurologic, or hematologic conditions may be more sensitive to the effects of EGME exposure (Reprotext, 1999).

Chemical: Persons exposed to other bone marrow suppressants or substances affecting the nervous system may be more sensitive to the effects of EGME exposure (Reprotext, 1999).

V. Acute Toxicity to Laboratory Animals

A 7-hour LC_{50} in mice of 1,480 ppm (4,736 mg/m³) was reported (Werner *et al*., 1943). Rats were exposed to 100, 300, or 1,000 ppm (320, 960, or 3,200 mg/m³) EGME for 6 hours per day for 9 days (Miller *et al*., 1981). Reduced bone marrow cellularity, severe degeneration and necrosis of the germinal epithelium in the testes, and severe lymphoid depletion in the cortex of the thymus were observed at necropsy following exposure to 1,000 ppm (3,200 mg/m³) EGME. Red and white blood cell counts and hemoglobin levels were significantly reduced in female rats exposed to 300 or 1,000 ppm, and in male rats exposed to 100, 300, or 1,000 ppm EGME.

Methoxyacetic acid and carbon dioxide were the main metabolites measured in the urine, feces and exhaled air of male rats following oral exposure to EGME (Miller *et al*., 1983). The majority of the metabolites were recovered in the urine, with smaller amounts in the exhaled air and feces.

VI. Reproductive or Developmental Toxicity

EGME is listed under California Proposition 65 (Cal/EPA, Safe Drinking Water and Toxic Enforcement Act of 1986) as a reproductive hazard with male reproductive toxicity and developmental endpoints.

Hanley and colleagues (1984) exposed pregnant rats and rabbits to 3, 10, or 50 ppm (9.6, 32, or 160 mg/m³) EGME for 6 hours per day on days 6-15 (rats) or 6-18 (rabbits) of gestation. Pregnant mice were exposed to 10 or 50 ppm (32 or 160 mg/m³) EGME for 6 hours per day on days 6-15 of gestation. A statistically significant increase in the incidence of skeletal variations was observed in rats and mice following maternal exposure to 50 ppm EGME. Gross soft tissue and skeletal teratogenic effects and significantly decreased fetal body weights were observed in rabbits following maternal exposure to 50 ppm EGME. In rabbits, a significant increase in the rate of fetal resorption was observed in the 10 ppm exposure group. Thus 10 ppm was considered a LOAEL for increased resorptions and 3 ppm a NOAEL. Although the authors

attribute the statistical significance of this effect to an unusually low rate of resorptions in controls compared to historical controls, historical control data were not presented.

Maternal toxicity as indicated by decreased body weight gain was observed in all three species exposed to 50 ppm. Pregnant rats exposed to EGME exhibited statistically significant lower mean hemoglobin levels and packed cell volumes at all 3 exposure levels. Thus 3 ppm was selected as a LOAEL for these 2 hematologic effects. A NOAEL was not identified. A lower mean red blood cell count was observed in rat dams exposed to 50 ppm EGME.

In another study, male rats were exposed to 30, 100, and 300 ppm (96, 320, and 960 mg/m^3) EGME for 6 hours per day, 5 days per week for 13 weeks before mating with unexposed female rats (Rao *et al*., 1983). A decrease in fertility, body and testes weights, and an increase in the incidence of gross and microscopic testicular and epididymal lesions were observed in the male rats exposed to 300 ppm (960 mg/m^3). Complete resorption of all fetuses was observed in the unexposed females mated with the males exposed to 300 ppm EGME. A male reproductive NOAEL of 100 ppm (320 mg/m^3) EGME was observed.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Level Protective against Mild Adverse Effects: Because the most sensitive effect observed is developmental toxicity, a severe adverse effect, and since this effect is observed at or below the threshold for a less serious effect, no mild adverse effect level is recommended.

Reference Exposure Level for 6 hr exposure (Protective Against Severe Adverse Effects): 0.03 ppm (93 μg/m^3)

Study	Hanley *et al*., 1984
Study population	pregnant rabbits
Exposure method	inhalation of 3, 10, or 50 ppm EGME 6 hours per day on days 6-15 of gestation
Critical effects	gross soft tissue and skeletal teratogenic effects and significantly decreased fetal body weights
LOAEL	10 ppm
NOAEL	3 ppm
Exposure duration	6 hours
LOAEL uncertainty factor	1
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Reference Exposure Level	0.03 ppm (0.093 mg/m^3; 93 μg/m^3)

Pregnant rabbits were exposed to 3, 10, or 50 ppm EGME 6 hours per day on days 6-18 of gestation (Hanley *et al*., 1984). Maternal toxicity, as indicated by decreased body weight gain, was observed only in rabbits exposed to 50 ppm EGME. The authors report that the hematologic

parameters of EGME exposed rabbits were not altered at any dose. Gross soft tissue and skeletal teratogenic effects and significantly decreased fetal body weight were observed in rabbits following maternal exposure to 50 ppm EGME. Statistically significant increases in fetal resorption rates were observed following maternal exposure to 10 or 50 ppm EGME. A NOAEL of 3 ppm for increased resorptions was used to develop the REL. An uncertainty factor of 100 was applied to account for inter- and intraspecies differences. Dividing this by 100 gives a level protective against severe adverse effects for a 6 hour exposure of 0.03 ppm (0.093 mg/m^3; 93 $\mu g/m^3$).

Level Protective Against Life-threatening Effects

Mice were exposed to EGME at concentrations of 930 to 6,800 ppm for a single 7-hour exposure (Werner *et al*., 1943). The mortality during exposure and up to three weeks following were recorded. The NOAEL was 930 ppm and was extrapolated from 7-hour to 1-hour exposure using a modification of Haber's equation, $C^n * T = K$, where n = 2. An uncertainty factor (UF) of 100 was applied to the time-adjusted NOAEL of 2,461 ppm to account for interspecies variability and individual human variation. The final 1-hour level protective against life-threatening effects for EGME is 25 ppm. (A benchmark dose approach (Crump, 1984; Crump and Howe, 1983) could not be employed because log-normal probit analysis of the lethality data was shown to be too heterogeneous.)

NIOSH (1995) lists an IDLH of 200 ppm derived by multiplying the current NIOSH REL of 0.1 ppm by 2,000, an assigned protection factor for respirators.

VIII. References

(ACGIH) American Conference of Governmental Industrial Hygienists. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Cincinnati (OH): ACGIH; 1991. p. 913-921.

Amoore JE, Hautala E. Odor as an aid to chemical safety: odor thresholds for compounds with threshold limit values and volatilities for 24 industrial chemicals in air and water dilution. J Appl Toxicol 1983;3(6):272-290.

Cohen R. Reversible subacute ethylene glycol monomethyl ether toxicity associated with microfilm production. A case report. Am J Ind Med 1984;6:441-446.

Crump KS. A new method for determining allowable daily intakes. Fundam Appl Toxicol 1984;4:854-871.

Crump KS, Howe R. Probit-A computer program to extrapolate quantile animal toxicological data to low doses. Ruston (LA): KS Crump & Company Inc.; 1983.

Groeseneken D, Veulemans H, Masschelein R, Van Vlem E. Experimental human exposure to ethylene glycol monomethyl ether. Int Arch Occup Environ Health 1989;61:243-7.

Hanley TR Jr, Yano BL, Nitschke KD, John JA. Comparison of the teratogenic potential of inhaled ethylene glycol monomethyl ether in rats, mice, and rabbits. Toxicol Appl Pharmacol 1984;75:409-422.

(HSDB) Hazardous Substances Data Bank. National Library of Medicine, Bethesda (MD) (CD-ROM Version). Denver (CO): Micromedex, Inc.; 1994. (Edition expires 4/30/94).

Miller RR, Ayres JA, Calhoun LL, Young JT, McKenna MJ. Comparative short-term inhalation toxicity of ethylene glycol monomethyl ether and propylene glycol monomethyl ether in rats and mice. Toxicol Appl Pharmacol 1981;61:368-377.

Miller RR, Hermann EA, Largvardt PW, McKenna MJ, Schwetz BA. Comparative metabolism and disposition of ethylene glycol monomethyl ether and propylene glycol monomethyl ether in male rats. Toxicol Appl Pharmacol 1983;67:229-237.

(NIOSH) National Institute for Occupational Safety and Health. Chemical listing and documentation of revised IDLH values. 1995. (http://www.cdc.gov/niosh/intridl4.html)

Rao KS, Cobel-Geard SR, Young JT, Hanley TR Jr, Hayes WC, John JA. Ethylene glycol monomethyl ether. II. Reproductive and dominant lethal studies in rats. Fundam Appl Toxicol 1983;3:80-85.

Reprotext® System. Dabney BJ, editor. Denver (CO): Micromedex, Inc.; 1999. (Edition expires 1/31/1999).

Ten Berge WF, Zwart A, Appelman LM. Concentration-time mortality response relationship of irritant and systemically acting vapors and gases. J Hazard Mater 1983;13:301-309.

Werner HW, Mitchell JL, Miller JW, Von Oettingen WF. The acute toxicity of vapors of several monoalkyl ethers of ethylene glycol. J Ind Hyg Toxicol 1943;25:157-163.